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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/574,688	04/05/2006	Takumi Takeyasu	Q94159	3724
23373 7590 05/29/2007 SUGHRUE MION, PLLC 2100 PENNSYLVANIA AVENUE, N.W. SUITE 800 WASHINGTON, DC 20037				
			EXAMINER HAVLIN, ROBERT H	
			ART UNIT 1609	PAPER NUMBER
			MAIL DATE 05/29/2007	DELIVERY MODE PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/574,688

Applicant(s)

TAKEYASU ET AL.

Examiner

Robert Havlin

Art Unit

1609

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 05 April 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-52 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-52 is/are rejected.
- 7) ☒ Claim(s) 1, 9, 45 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner. _____
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date 7/25/06, 4/5/06.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

Art Unit: 1609

DETAILED ACTION

Claims 1-52 are currently pending.

Information Disclosure Statement

Applicant's IDS, filed on 4/5/06 and 7/25/06 have been considered.

Priority

This application is a 371 of PCT/JP04/15186 filed on 10/07/2004 and claims foreign priority to JAPAN 2003-349318 (10/08/2003), JAPAN 2003-350441 (10/09/2003), and JAPAN 2003-350439 (10/09/2003).

Claim Rejections - 35 USC § 102

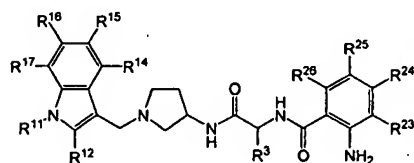
1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

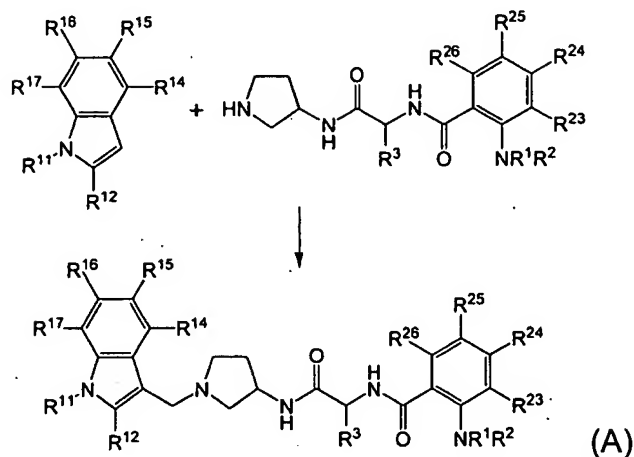
2. Claims 1-5, 7-14, and 32-44 are rejected under 35 U.S.C. 102(b) as being anticipated by Shiota et al. (EP 1179341-A1).

The claims are drawn to methods for synthesizing a compound of the formula

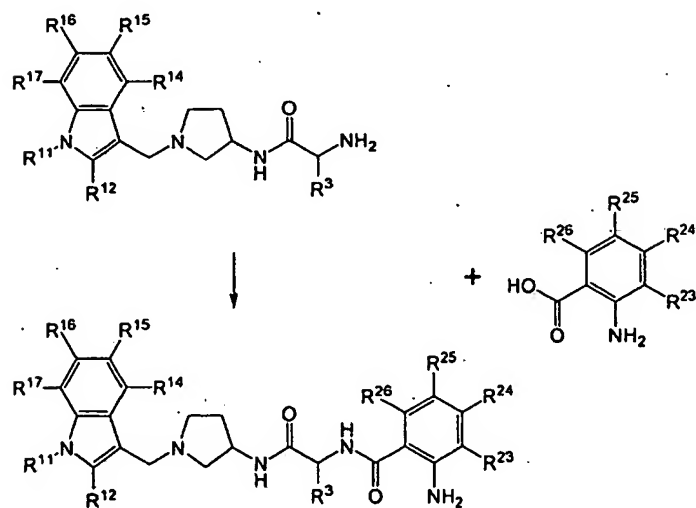


(i) via the two processes below:

Art Unit: 1609



and

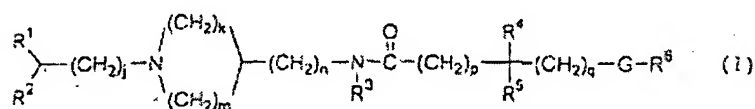


groups for R1 and R2 (claims 2 and 3), synthetic equivalents (synthons), deprotection steps, condensing agents, additives, and solvents. In addition, the claims are drawn to a compound of formula III which is a precursor to the final product produced with the claimed method referred to above.

Shiota et al. teaches the coupling of reaction (A) above on pages 218 (line 55) - 219 (line 50) in "preparation process" 2 and 3 for the species of compounds 2235 and

Art Unit: 1609

2241 on page 215 corresponding to formula (I)



in the following manner:

Table 1.204

Compd. No.	$\begin{array}{c} \text{R}^1 \\ \diagdown \\ \text{---}(\text{CH}_2)_j\text{---} \\ \diagup \\ \text{R}^2 \end{array}$	k	m	n	chirality	R ³	$\begin{array}{c} \text{R}^4 \\ \\ \text{---}(\text{CH}_2)_p\text{---} \text{---}(\text{CH}_2)_q\text{---G---R}^6 \\ \\ \text{R}^5 \end{array}$
2235		1	2	0	R	H	
2241		1	2	0	R	H	

Shiota et al. also teaches the protection/deprotection of reactive functional groups such as amines on page 221 (line 1-17) and specifically uses t-butoxycarbonyl in numerous examples including reference example 1 of page 221, line 26. On page 246 in example 749 the method of removing a protecting group using HCl in organic solvent is taught.

Preparation process 3 teaches the coupling method of reacting an aldehyde of indole (formula VI) with the compound of formula V. Although the reference does not specifically teach the use of a "synthon of formaldehyde" or formalin in combination with indole, since a synthon is by definition a synthetic equivalent, and in this case would be anything equivalent to formaldehyde, the teachings of the process are equivalent to the use of a synthon of formaldehyde. Moreover, the compound of formula VI on page 219 of the reference is an intermediate and is equivalent to any formalin synthon.

Art Unit: 1609

Shiota et al. teaches the coupling reaction (B) from above in preparation process 4 on pages 219-220 with the use of the condensing agent of DCC (1,3-dicyclohexylcarbodiimide) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (page 218, line 45). The reference also teaches the use of the additive 1-hydroxy-1,2,3-benzotriazole (HOBt) in the same reaction as well as the use of triethylamine on page 218.

Shiota et al. teaches on page 218, compounds of the formula III which anticipate the compounds of claims 37-44 when taken with the selection of the variables for the two species of compounds 2235 and 2241.

Therefore, Shiota et al. anticipates claims 1-5, 7-14, and 32-44.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

4. Claims 1-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shiota et al. in view of Katritzky et al. (J. Org. Chem. 1990, v55, p3688-3691) and Schelhaas et al. (Angew. Chem. Int. Ed., 1996, v35, p2056-2083).

Determination of the scope and content of the prior art (MPEP 2141.01)

The claims are drawn to methods of making compounds as recited above in addition to further detailed protection/coupling/deprotection steps with the use of specific reagents.

Art Unit: 1609

Shiota et al. teaches several specific products and methods of making including species which anticipate the genus of the instantly claimed methods.

Katritzky et al. teaches the use of dialkylaminomethyl groups for use as a protecting group on indole.

Schelhaas et al. teaches general protecting group strategies and steps to optimize the production of a desired product having reactive groups such as amines and amides in the final product.

Differences between the prior art and the claims and finding of prima facie obviousness

(MPEP 2141.02 and 2142-2143)

Shiota et al. teaches all of the elements of claim 6 as described above, but does not specifically select a dialkylaminomethyl protecting group on the indole. Katritzky et al. teaches the use of dialkylaminomethyl protecting groups for substituted indole synthesis, including the specific N,N-dimethylaminomethyl-indole intermediate in addition to gramine and isogramine on page 3689. Since the chemistry of indoles and the use of protecting groups are well known in the art when one of ordinary skill in the art would attempt to synthesize the compounds of the claimed method they would have a reasonable expectation of success to arrive at the specific combination of the particular protecting group for the indole.

Claims 15 and 16 differ from the teachings of Shiota et al. only by the specific recitation of the amine deprotection step described in "reaction step 4". Schellhaas et al. teaches the use of acid-labile protecting groups on page 2059 in organic synthesis and cites that the methods reviewed are "acid-mediated-hydrolysis is one of

Art Unit: 1609

the best established methods in protecting group chemistry and forms one of the central pillars of the subject". Therefore, one of ordinary skill in the art would have been motivated to use protecting group chemistry to protect the reactive amine (as suggested by Shiota et al.) and further selected acid hydrolysis with HCl in an organic solvent using the well-known teachings of Schelhaas et al. when confronted with the challenge of the stepwise synthesis of the product disclosed in Schelhaas et al.

Claims 17-20 differ from the teachings of Shiota et al. only by the rearrangement of the steps of the two couplings of (A) and (B) such that a simpler starting material is used, namely the reactant of "reaction step 3". However, recombining the two synthetic coupling steps taught by Shiota et al. to start with a cheaper and simpler starting material would have been obvious to one of ordinary skill in the art.

Claims 21-23 adds "reaction step 2" to the aforementioned overall reaction which differs merely by the process of removing of a benzyl protecting group from the reactive amine on the precursor. Therefore, one of ordinary skill in the art would have been motivated to use protecting group chemistry to protect the reactive amine (as suggested by Shiota et al.) and further selected a benzyl protecting group and removed it using hydrogen with a palladium catalyst using the well-known teachings of Schelhaas et al. when confronted with the challenge of the stepwise synthesis of the product disclosed in Schelhaas et al.

Claims 24-31 correspond to the identical coupling step as taught in "preparation process 1" on page 218 of Shiota et al. with the difference of the starting materials having been decomposed into simpler components. As recited above, one of ordinary

Art Unit: 1609

skill in the art would be motivated to select simple starting materials such as those of the reactants of "reaction step 1" due to lower cost and ready availability from commercial sources and combined them in the manner claimed to produce the product disclosed in Shiota et al. Therefore, the reaction step method and the selection of the same coupling agents, solvents, and additives as disclosed by Shiota et al. would have been obvious to one of ordinary skill in the art.

Claims 45-52 are drawn to a method of making a compound of formula IV. Shiota et al. teaches the coupling reaction described in claim 45 in the "preparation process 6" on page 220 of the reference, with the difference of a simpler starting material. One of ordinary skill in the art would have been motivated to divide the overall synthesis taught in Shiota et al. into a multistep synthesis using the identical coupling reaction step of Shiota et al. such that cheaper, readily available reactants are used. Thus the claims are obvious.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 4, 5, 18, and 19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims are drawn to subject

Art Unit: 1609

matter which is described as a "synthon of formaldehyde" which in claim 5 is selected from formalin, paraformaldehyde and trioxane. The term synthon generally refers to a synthetic equivalent which can take on a huge number of possible definitions in a given synthetic process. In the instant specification, there exists no guidance as to the boundaries of the scope of the claims and apparently the only synthon used is formalin in Example 15. Thus, there is no written description suggesting that the applicant actually had possession of the claimed invention beyond the one example provided.

Claim Objections

Claim 1, 9, and 45 are objected to for having unclear language in reference to the preamble and the inclusion of a formula. For example, the examiner recommends rephrasing claim 1 to be:

1. *A method of producing aminopyrrolidine derivatives of **formula (I)** or salts thereof comprising reaction steps 1 and 2...*

Conclusion

All claims are rejected.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert Havlin whose telephone number is (571) 272-9066. The examiner can normally be reached on Mon. - Fri., 7:30am-5pm EST.

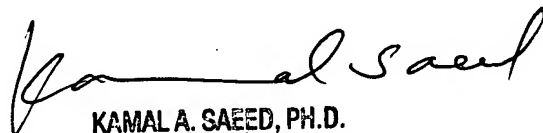
If attempts to reach the examiner by telephone are unsuccessful the examiner's supervisor, Cecilia Tsang can be reached at (571)-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Art Unit: 1609

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Robert Havlin
Examiner

RH



KAMAL A. SAEED, PH.D.
PRIMARY EXAMINER